Office Action Summary	Application No.	Applicant(s)	
	10/510,411	ZAGHOUANI ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47,49,50,54-59 and 61-65* is/are pending in the application.

4a) Of the above claim(s) *49,50 and 62-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47,54-59 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *attached*.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 5/12/09 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment, remarks, 1.132 declaration of Inventor Zaghouani, and IDS filed 5/12/09 have been entered.

Claims 49, 50, and 62-65 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 47, 54-59 and 61 are under examination.

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 47, 48, 54-59 and 61 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/30706 (IDS) in view of Liu et al. (2000).

As set forth previously, WO 98/30706 teaches an engineered fusion protein for the treatment of IDDM, in particular, a humanized IgG_{2b} chimeric protein wherein an autoantigen peptide is inserted into the D segment of a CDR3 loop, further including a soluble pharmaceutical composition of the construct (see particularly Figure 1, page 13, and Example II).

The reference teaching differs from the claimed invention only in that it does not teach Ig-chimera constructs comprising the GAD peptides of SEQ ID NOS:3 and 4.

Liu et al. teaches that the peptides of SEQ ID NOS:3 and 4 comprise known T cell epitopes (see particularly page 14597, column 1 paragraph). The reference also teaches that the epitopes are thought to be involved in the diabetogenic process (see particularly page 14596, paragraph spanning columns 1 and 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce the construct of WO 98/30706 employing the T cell epitopes of SEQ ID NOS:3 and 4, as taught by Liu et al. One of ordinary skill in the art at the time the invention was made would have been motivated to use the epitopes of Liu et al. because they were thought to be involved in the diabetogenic process and thus, suitable for use in the constructs of the instant claims.

Applicant's arguments, filed 5/12/09, have been fully considered but are not found persuasive. Applicant argues that the references do not teach a soluble Ig construct.

Absent additional manipulation of some sort the constructs of WO 98/30706 would be soluble. Antibodies are inherently soluble unless attached to a solid support or aggregated. Indeed, antibody tails are routinely added to less soluble proteins to increase their solubility. Additionally, it is well known that when blood is clotted the liquid fraction is referred to as serum. Said fraction derived from an immunized individual is referred to as anti-serum because it contains soluble antibodies to the immunizing agent.

Applicant argues that Liu et al. teach away from the claimed invention.

This issue has been addressed previously. In the Advisory Action of 2/26/09, "A review of the reference does not support Applicant's position. As set forth previously the reference flatly states that the peptides employed (comprising the sequences employed in the instant Ig construct) are immunodominant in type 1 diabetes. The bulk of the Discussion is given to consideration of problems with the reference's tetramer technology. The prospective problems include contamination and peptide configurations that are suboptimal. On the other hand, Applicant's own work, i.e., WO 98/30706 teaches that the Ig-chimera constructs of the instant claims (into which the peptides of Liu et al. could be fitted) would be useful for many antigen applications, specifically including use in T cell mediated disorders such as type 1 diabetes (page 10). Accordingly, Applicant's own work provides every expectation of success."

Note that Applicant's incomplete quote from page 1460, column 1 (regarding the tetramers' possible lack of affinity as contributing to the low level of measured response) is not further persuasive. Overall the reference takes no position

that the p206 peptide is *not* immunodominant as the reference cites Chao and McDevitt (1997) wherein those investigators found the peptide to be the *most* immunodominant GAD65 peptide known.

Applicant asserts unexpected results, arguing that the restoration of normoglycemia would not be expected employing a single antigenic construct because type 1 diabetes involves multiple antigens and T cell actions.

Applicant's argument is not persuasive given the instant Inventor's own success in treating other multi-antigenic diseases, e.g., EAE with single antigenic constructs in other animal models. See for example WO 98/30706. See also the results of the instant specification wherein the Inventor reports efficacy employing just an Ig-INS construct.

Applicant argues that soluble Ig-peptide constructs would not have been expected to treat or delay type 1 diabetes.

Applicant's argument is again not persuasive given the fact that in the instant application the soluble Ig-INS is generally as effective, if not more so, than an aggregated Ig-INS construct in the treatment of diabetes.

Applicant argues that the Inventor's declaration shows the unexpected property of the Ig-GAD2 construct's ability to actually increase the number of healthy islet cells.

The Inventor's declaration will be addressed here.

First note that no rejection has been made regarding the effectiveness of the Ig-GAD2 construct in treating type 1 diabetes in NOD mice by the method of Section 7 of the Inventor's declaration. Given that the Inventor's similar constructs had similar results in treating both EAE in ISJL/J mice (with an Ig-PLP construct, WO 98/30706) and type 1 diabetes in NOD mice (with an Ig-INS construct, the instant specification) treatment of disease itself in experimental mice cannot be found to be unexpected. However, the Inventor asserts results that would be unexpected, i.e., the actual regeneration of healthy islets in diabetic mice. Thus, the declaration will be considered with this result in mind.

Upon review of the declaration it is noted that the experiments reported therein are sometimes described incompletely or inadequately. For example, at Section 7 there in no indication of how many mice were included in each of the

experimental groups. At Figure 1B there is no figure legend. Figure 2 is of such poor quality that no conclusion can be drawn therefrom. Again at Figure 3 it is not disclosed how many mice comprised each of the 3 experimental groups. Presumably the groups comprised more than a single mouse each, yet the graphs show no error bars. Additionally, there is an unexplained asterisk over the "15 wk treated" bar. The horizontal axis of Figure 4 has no numbers on it and the explanation of the Figure's significance in Section 11 is not understood. It is unclear what Figure 5 represents, what tissue it comprises, and what the single arrow points to. Again the quality of Figures 6, 8, and 9 are such that no conclusions can be drawn therefrom and it is not disclosed what the arrows point to. Of particular interest are the BrdU proliferation experiments of Sections 13-15 (because the result of the regeneration of healthy islets in diabetic mice would be truly unexpected). But these are not adequately described nor are the results of Figure 7 interpretable. For example, again, how many mice were involved. When were they injected with BrdU? In Figure 7, does the figure mean that 10 cells were found in treated mice? Further in Figure 7, what is the meaning of the 2 asterisks over the "Treated" bar. And again, in the experiments of Sections 15-19 it is not disclosed how many mice were involved nor are the results of Figures 10 and 11 adequately explained. Finally, is the "IL-27" of Section 18 merely a typographical error? The Inventor is advised that if these figures were taken from published references it might be more expedient to simply submit the references.

In total then, the details and results disclosed in the instant declaration are not found persuasive of the surprising and unexpected results asserted by the Inventor in Sections 25-28 of the declaration.

4. No claim is allowed.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571)272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on (571) 272-0878.

6. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

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